REMARKS

Claims 1, 4-6, 8-14, 18-21, 25-27, 29, 31 and 35-39 were pending in this application. Claims 8, 11, 14, 21, 26, 27, 29, 31 and 35-39 are cancelled herein without prejudice. Thus, after entry of this amendment, **claims 1, 4-6, 9, 10, 12, 13, 18-20 and 25 will be pending**.

The claims are amended herein to be commensurate in scope with the Declaration submitted June 5, 2008, which provides evidence of the unexpectedly superior results obtained using the claimed methods. In particular, claims 1 and 25 are amended to specify that the subject is administered an effective amount of "an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 176, an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 177 and an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 178." Support for this amendment can be found, for example, in claims 27, 29, 31 and 35-39 (cancelled herein) and in Example 8 of the specification, beginning on page 45, which describes administration of the combination of the three recited oligodeoxynucleotides. The amendments to claims 9, 10, 12 and 13 specify particular nucleotides that have phosphodiester or phosphorothioate bases to properly depend from claim 1. Support for the amendments to claims 9, 10, 12 and 13 can be found, for example, at page 24, line 18 to page 26, line 6; and page 45, lines 20-28, of the specification. Claim 19 is amended to correct dependency.

No new matter is introduced by these amendments. Reconsideration of the application is respectfully requested in view of the foregoing amendments and following remarks.

Examiner Interviews

Applicants thank Examiner Horning for the courtesy of a telephone interview with Applicants' representative, Susan Alpert Siegel, on January 5, 2011. During the telephone call, amending the claims to recite the specific combination of oligodeoxynucleotides (SEQ ID NO: 176, SEQ ID NO: 177 and SEQ ID NO: 178) used in the experiments described in the Declaration submitted June 5, 2008, was discussed. Applicants also thank Examiner Horning for the telephone call of January 10, 2011 with Applicants' representative, Jodi L. Connolly, during which draft claim amendments were discussed. Examiner Horning indicated that amending claim 1 to require administration of all three oligodeoxynucleotides would require further search

and consideration because SEQ ID NO: 178 had not yet been searched. Therefore, Applicants submit herewith a Request for Continued Examination to allow for the search of SEQ ID NO: 178.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 4-6, 8-14, 18-21, 25-27, 29, 36 and 38 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Klinman (PCT Publication No. WO 00/61151), Cho *et al.* (*Nature Biotechnology,* 2000), Alvar *et al.* (*Clinical Microbiology Reviews* 10(2):298-319, 1997), and de la Rosa *et al.* (*Journal of Clinical Microbiology* 40(3):762-767, 2002). Claims 8, 11, 14, 21, 26, 27, 29, 36 and 38 are cancelled herein, rendering the rejection moot as it pertains to these claims. Applicants traverse the rejection as it applies to claims 1, 4-6, 9, 10, 12, 13, 18-20 and 25.

A *prima facie* case of obviousness has not been established

As amended herein, independent claims 1 and 25 specify that a combination of immunostimulatory D oligodeoxynucleotides is administered to an immunocompromised subject infected with HIV or SIV, and secondarily infected with *Leishmania*, and the combination includes an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 176, an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 177 and an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 178.

Although Klinman teaches each of the individual oligodeoxynucleotide (ODN) sequences recited in the claims (SEQ ID NOs: 32, 37 and 42 of Klinman correspond to SEQ ID NOs: 176, 177 and 178, respectively), Klinman does not teach or even suggest co-administration of the three recited ODNs. In fact, Klinman does not teach or suggest administering any combination of ODNs – the disclosure is limited to administration of a single ODN. Moreover, as the Office admits on page 5 of the Office action, Klinman does not teach a method of increasing an immune response to an opportunistic *Leishmania* infection in an immunocompromised individual having HIV-1, HIV-2 or AIDS. Cho *et al.*, Alvar *et al.*, and de la Rosa *et al.* do not cure the deficiencies of Klinman at least because none of these references teach or suggest administration of a combination of immunostimulatory D ODNs, or more particularly, administration of a combination of ODNs comprising the nucleic acid sequences of SEQ ID NO: 176, SEQ ID NO: 177 and SEQ ID NO: 178, as recited in the pending claims.

Since the combination of cited references does not teach each and every element of the pending claims, a *prima facie* case of obviousness has not been established.

The claimed methods exhibit unexpectedly superior results

Even if the Office maintains that the pending claims are *prima facie* obvious, Applicants submit that the claimed methods provide unexpectedly superior results, as discussed at length in the Declaration under 37 C.F.R. § 1.132 (submitted with the response filed on June 5, 2008), the response filed January 2, 2009, the response filed July 17, 2009, the response filed January 4, 2010, and the response filed July 13, 2010. Applicants have not reiterated all of the previously submitted arguments. However, the most pertinent aspects of the prior responses are provided below for the Examiner's convenience. Applicants further note that as amended, the pending claims are commensurate in scope with the Declaration submitted June 5, 2008.

Pages 4-5 of the Declaration describe the results obtained when a combination of D ODNs (D19 – SEQ ID NO: 176; D35 – SEQ ID NO: 177; and D29 – SEQ ID NO; 178) were evaluated in an art-accepted macaque model of HIV. Macaques that had been infected for greater than 12 months with SIV Mac239, and had viral loads ranging from 0.3-28 x 10^6 copies/ml, were used in these studies. The animals were stratified based on viral load and then challenged with *L. major* metacyclic promastigotes (MHOM/IL/80/Friedlin). Healthy macaques challenged with *L. major* developed cutaneous lesions characterized by erythema, induration and ulceration that peaked 25 days after challenge and resolved within 50 days (see Fig. 3A of the Declaration). Due to their immunosuppressed state, untreated macaques developed severe progressive cutaneous lesions that did not resolve. The severity of *Leishmania* infection in SIV-infected animals treated with K ODN was not significantly different from that of the controls.

In contrast, SIV-infected macaques treated with the combination of D ODN as recited in pending claims 1 and 25, developed significantly smaller lesions, and their infection did not progress over time (Fig. 3A of the Declaration) as compared to controls. The animals were euthanized on day 56, and their parasite burden measured. SIV-infected monkeys treated with D ODN had a 35-fold reduction in total parasite burden at the lesion site compared to SIV-infected animals treated with control ODN or saline (see Fig. 3B of the Declaration, $p<0.001$). The comparative data, both with regard to the type of ODN used (D versus K), and the type of

immune response achieved (general response versus a response to a secondary infection) demonstrate the unexpectedly superior result that is achieved using the claimed methods.

Verthelyi *et al.* (*J. Immunol.* 170: 4717-4723, 2003; of record) provides additional evidence of the superior results achieved with the claimed methods. This post-filing date publication provides additional evidence that the specific combination of D ODNs recited in the pending claims can be used to induce an immune response to *Leishmania* in macaques infected with an immunodeficiency virus (SIV). Macaques treated with the D ODNs developed significantly smaller lesions, and their infection did not progress over time. However, the severity of *Leishmania* infection in animals treated with immunostimulatory K ODNs was not significantly different than controls. Monkeys treated with the claimed combination of D ODNs had a 35-fold reduction in parasite burden at the lesion site. This provides additional evidence of the unexpectedly superior results achieved using the claimed methods.

Summary

The combination of cited references fails to teach each and every element of the pending claims, thus a *prima facie* case of obviousness has not been established. Moreover, the documentation of an unexpectedly superior result overcomes any *prima facie* case of obviousness based on the cited references. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Request for Interview

Applicants have made every effort to place the present application in condition for allowance. If any matters remain to be discussed before a Notice of Allowance is issued, Examiner Horning is respectfully requested to contact the undersigned for a telephone interview at the telephone number listed below.

Conclusion

Applicants believe the present application is ready for allowance, which action is requested. A written request for an interview is provided in this Amendment.

Respectfully submitted,

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